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POHNERT, STEVEN C	
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1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)
	10/801,956	FUJIMOTO ET AL.
	Examiner	Art Unit
	STEVEN POHNERT	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *103-132* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *103-132* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 June 2011* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☐ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

DETAILED ACTION

Claim status and Formal matters

This action is in response to papers filed 6/9/2011.

The response has amended claims103, 109, 115, 118, 124, and 127.

The written description and 112-2nd rejections have been withdrawn in view of the amendment.

Response to Amendment

1. The declaration of Hoon under 37 CFR 1.132 filed 6/9/2011 is insufficient to overcome the rejection of claims 103-132 based upon Soegnas and Fujiwara as set forth in the last Office action because: It does not provide evidence of an unpredicted result. The declaration id by a con-inventor of the application. The response presents assertions that individuals not affected with cancer have circulating accellular DNA. The response asserts there is evidence in the last paragraph of Fujiwara, however, the last paragraph states, "the study demonstrated that multiple LOH markers can be detected in the plasma of melanoma patients and not healthy donors." Thus this does not indicate that healthy individuals have accellular DNA as asserted. The response directs the examiner to the paragraph bridging the 1st and 2nd columns of 6724 of Taback, which again merely indicates that there was no LOH in normal donors. The response further directs the examiner to Fujimoto which provides further contentions. While Fujiwara teaches on page 1570 that"previous studies revealed that serum of cancer patients contains approximately two to four times the amount of free DNA as that of normal donors," this does not demonstrate the DNA content is diploid as asserted or is

an adequate control, as the response has provided no evidence that the use of "any" human control DNA would allow for adequate determination of LOH.

The response continues by asserting the control DNA can be prepared from non-neoplastic tissue from the same patient or from the biological fluid or tissue from a normal person. While the specification suggests these sources of control DNA can be obtained it does not define control DNA as only from these sources. Further the specification does not specifically define what a normal or healthy individual is. A person in not diagnosed with a cancer or other disease would be considered healthy and according to Fujiwara could have a 2 to 4 fold increase in accellular DNA thus resulting in a determination that another healthy subject has LOH of all alleles, thus making the claimed method unpredictable.

The response continues by indicating that stage I and II melanoma do not have metastasis. The response further continues by indicating the example of the application has disclosed biochemotherapy. The examiner concurs. The response further asserts that the results of biochemotherapy would readily be applicable to other treatments. MPEP 716.01 (c) states: "In assessing the probative value of an expert opinion, the examiner must consider the nature of the matter sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion." MPEP 716.01 (c) further states, "Although factual evidence is preferable to opinion testimony, such testimony is entitled to consideration and some weight so long as the opinion is not on the ultimate legal conclusion at issue. While an opinion as to a legal conclusion is not

entitled to any weight, the underlying basis for the opinion may be persuasive." Finally, MPEP 716.01 (C) states, "An affidavit of an applicant as to the advantages of his or her claimed invention, while less persuasive than that of a disinterested person, cannot be disregarded for this reason alone." Thus these are opinion of applicant that have not been substantiated by any evidence and thus are not persuasive. Further the teachings of O'Day, Chapman and Healy demonstrates different efficacy of different therapeutics, thus providing evidence contrary to the assertion of applicant.

The declaration continues by indicating the Soegnas teaches LOH of the claimed markers in melanoma samples. The response continues by incorrectly asserting the examiner questions whether one of skill in the art could predict or assume that LOH of the microsatellite DNA markers in metastatic melanoma tumors and accellular DNA from patients with metastatic melanoma. This argument is not persuasive as the 103 rejection presented indicates the prior art suggests this relationship is obvious contrary to the assertion of the declaration.

The response continues by indicating Soegnas incorrectly identified the markers as being associated with APAF1. These arguments are beyond the scope of the claimed invention as Soegnas teaches LOH of the markers in metastatic melanoma samples.

The declaration continues by providing the opinion of the applicant that one of skill in the art could not predict microsatellite markers in the serum or plasma of melanoma patients are the same as in the tumor. This argument appears to be the opinion of applicant that has not been substantiated by any evidence. Further the

response earlier appeared to assert that there is accellular DNA in all human subjects, which seems to contradict this statement. Further the claims are to LOH and not the presence of markers in accellular DNA. Finally, the claims are drawn to the loss of one of more markers. The declaration on page 7 indicates that the skilled artisan recognizes that there is a significant correlation between LOH and AJCC stage with further conflicts with these assertions.

The response continues in point 10 to provide applicant's opinion on predictability of survival, prognosis, and therapy efficacy without providing evidence.

The response then reviews the teachings of Fujiwara and states, “we found a significant correlation between the number of LOH microsatellite markers with a patient’s plasma and AJCC stage in 76 patients.” This appears to demonstrate that the 103 of Soegnas and Fujiwara is predictable as the more LOH the higher the AJCC stage and the worse prognosis. The instant claims are drawn to correlating one or more LOH event, thus detecting all 4 claimed markers would be indicate of a later stage of melanoma, worse prognosis and survival. The arguments with respect to other specific markers and combination are not persuasive as they are beyond the scope of the claimed invention.

The response continues by providing applicant's opinion about unpredictability and with respect to specific markers. However the instant claims are drawn to the detection of one or markers, which does not exclude the detection of additional markers not specifically recited in the claims. Further the teachings of Fujiwara stating, “the frequency and number of microsatellite markers with LOH in plasma significantly

increased in more advanced clinical stages of disease" (1570). The arguments with respect to Taback are not persuasive as Taback states, "We and others have shown that as melanomas progress they acquire additional LOH events, which may be associated with a metastatic or more aggressive phenotype" (5725). Taback teaches there is a 91% correlation between plasma LOH marker detected and LOH in the corresponding tumor specimen was observed (5725). Taback like Fujiwara teaches, "The presence of LOH in the blood of melanoma patients is a common finding occurring in 56% of patients assessed. The increased incidence of LOH correlated significantly with advanced AJCC stage of disease" (5725).

The arguments with respect to D9S157 are beyond the scope of the claimed invention. Further the claims are drawn to one or more of LOH, applicants have provided no evidence that the detection of increased LOH in the plasma is not predictably associated with melanoma stage, progression and prognosis as suggested by the teachings of Taback and Fujiwara to which applicant is an author.

Thus these arguments are not persuasive.

Drawings

2. The drawings are objected to because the figures are not labeled consistent with 37 CFR 1.84 (u) (1) which requires The different views must be numbered in consecutive Arabic numerals, starting with 1,independent of the numbering of the sheets and, if possible, in the order in which they appear on the drawing sheet(s). Partial views intended to form one complete view, on one or several sheets, must be identified by the same number followed by a capital letter. View numbers must be

preceded by the abbreviation "FIG. " Where only a single view is used in an application to illustrate the claimed invention, it must not be numbered and the abbreviation "FIG. " must not appear.. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Response to Arguments

The replacement drawings do not recite, "FIG" as required by 37 CFR 1.84(u)(1) thus the objection is maintained.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 103-132 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A method of predicting metastatic melanoma survival comprising: providing a blood, serum or plasma sample containing acellular DNA from a human subject suffering from metastatic melanoma; comparing DNA markers selected from the group consisting of D12S1657, D12S393, D12S1706, and D12S346 in the acellular DNA with the same DNA markers in a control DNA from subject peripheral blood lymphocytes; determining from the comparison step if the acellular DNA has a loss of heterozygosity at one or more of the DNA markers; and predicting that the subject having a loss of heterozygosity at one or more of the DNA markers has a lower probability of survival that a subject with no loss of heterozygosity.

However, the specification and prior art do not reasonably provide enablement for comparison to any control sample. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

Claim 103 is drawn to a method of predicting metastatic melanoma survival comprising: providing a blood, serum or plasma sample containing acellular DNA from a human subject suffering from metastatic melanoma; comparing DNA markers selected from the group consisting of D12S1657, D12S393, D12S1706, and D12S346 in the acellular DNA with the same DNA markers in a control DNA; determining from the comparison step if the acellular DNA has a loss of heterozygosity at one or more of the DNA markers; and predicting that the subject having a loss of heterozygosity at one or more of the DNA markers has a lower probability of survival.

Thus claim 103 encompasses the loss of heterozygosity of one or more alleles of the claimed markers relative to any control from any species are indicative of a lower probability of survival.

Claim 104 depends from claim 103 and draws the invention to wherein the acellular and control DNA are amplified.

Claim 105 depends from claim 103 and draws the invention to wherein the control DNA is obtained from non- neoplastic tissue from the subject.

Claim 106 depends from claim 103 and draws the invention to wherein the control DNA is obtained from a biological fluid or tissue from a normal subject.

Thus claim 106 encompasses the use of control DNA from any "biological fluid" or "tissue" of any subject from any species.

Claim 107 depends from claim 103 and draws the invention to wherein the control DNA is obtained from peripheral blood lymphocytes from the subject.

Claim 108 depends from claim 103 and draws the invention to wherein the loss of heterozygosity comprises a 40% or more reduction of peak intensity for the acellular DNA marker as compared to the corresponding control DNA marker.

Independent claim 109 is drawn to a method of metastatic melanoma prognosis comprising: providing a blood, serum or plasma sample containing accellular DNA from a human subject suffering from metastatic melanoma;
comparing DNA markers selected from the group consisting of D12S1657, D12S393, D12S1706, and D12S346 in the acellular DNA with the same DNA markers in a control DNA; determining from the comparison step if the acellular DNA has a loss of heterozygosity at one or more of the DNA markers; and predicting that the subject having a loss of heterozygosity at one or more of the DNA markers has a poor prognosis.

Thus claim 109 encompasses the loss of heterozygosity of one or more alleles of the claimed markers relative to any control from any species are indicative of a lower probability of survival.

Claim 110 depends from claim 109 and draws the invention to wherein the acellular and control DNA are amplified.

Claim 111 depends from claim 109 and draws the invention to wherein the control DNA is obtained from non- neoplastic tissue from the subject.

Claim 112 depends from claim 109 and draws the invention to wherein the control DNA is obtained from a biological fluid or tissue from a normal subject.

Claim 113 depends from claim 109 and draws the invention to wherein the control DNA is obtained from peripheral blood lymphocytes from the subject.

Claim 114 depends from claim 109 and draws the invention to wherein the loss of heterozygosity comprises a 40% or more reduction of peak intensity for the acellular DNA marker as compared to the corresponding control DNA marker.

Independent claim 115 is drawn to a method of predicting efficacy of melanoma cancer therapy comprising: providing a blood, serum or plasma sample containing acellular DNA from a human subject suffering from Stage IV melanoma prior to administration of a cancer therapy; comparing DNA markers selected from the group consisting of D12S1657, D12S393, D12S1706, and D12S346 in the acellular DNA with the same DNA markers in a control DNA; determining from the comparison step if the acellular DNA has a loss of heterozygosity at one or more of the DNA markers; and

predicting that the cancer therapy efficacy of the subject having a loss of heterozygosity one or more of the DNA markers will likely be poor.

Claim 116 depends from claim 115 and draws the invention to wherein the cancer therapy is selected from the group consisting of chemotherapy, radiation therapy, gene therapy, immunotherapy, surgical procedure, and a combination of the cancer therapies.

Claim 117 depends from claim 115 and draws the invention to wherein the cancer therapy is biochemotherapy.

Claim 1118 depends from claim 117 and draws the invention to wherein the cancer therapy is biochemotherapy and is a combination selected from the group consisting of dacarbazine, cisplatin, vinblastin, interferon alpha-2b, IL-2, and tamoxifen.

Claim 119 depends from claim 115 and draws the invention to wherein the acellular and control DNA are amplified.

Claim 120 depends from claim 115 and draws the invention to wherein the control DNA is obtained from non- neoplastic tissue from the subject.

Claim 121 depends from claim 115 and draws the invention to wherein the control DNA is obtained from a biological fluid or tissue from a normal subject.

Claim 122 depends from claim 115 and draws the invention to wherein the control DNA is obtained from peripheral blood lymphocytes from the subject.

Claim 123 depends from claim 115 and draws the invention to wherein the loss of heterozygosity comprises a 40% or more reduction of peak intensity for the acellular DNA marker as compared to the corresponding control DNA marker.

Independent claim 124 is drawn to a method of predicting responsiveness to cancer therapy comprising: providing a blood, serum or plasma sample containing acellular DNA from a human subject suffering from Stage IV melanoma prior to administration of a cancer therapy; comparing DNA markers selected from the group consisting of D12S1657, D12S393, D12S1706, and D12S346 in the acellular DNA with the same DNA markers in a control DNA, determining from the comparison step if the acellular DNA has a loss of heterozygosity at one or more of the DNA markers; and predicting that the subject having a loss of heterozygosity at one or more of the DNA markers has a poor likelihood of responding to cancer therapy.

Claim 125 depends from claim 124 and draws the invention to wherein the cancer therapy is selected from the group consisting of chemotherapy, radiation therapy, gene therapy, immunotherapy, surgical procedure, and a combination of the cancer therapies.

Claim 126 depends from claim 124 and draws the invention to wherein the cancer therapy is biochemotherapy.

Claim 127 depends from claim 126 and draws the invention to wherein the cancer therapy is biochemotherapy and is a combination selected from the group consisting of dacarbazine, cisplatin, vinblastin, interferon alpha-2b, IL-2, and tamoxifen.

Claim 128 depends from claim 124 and draws the invention to wherein the acellular and control DNA are amplified.

Claim 129 depends from claim 124 and draws the invention to wherein the control DNA is obtained from non- neoplastic tissue from the subject.

Claim 130 depends from claim 124 and draws the invention to wherein the control DNA is obtained from a biological fluid or tissue from a normal subject.

Claim 131 depends from claim 124 and draws the invention to wherein the control DNA is obtained from peripheral blood lymphocytes from the subject.

Claim 132 depends from claim 124 and draws the invention to wherein the loss of heterozygosity comprises a 40% or more reduction of peak intensity for the acellular DNA marker as compared to the corresponding control DNA marker.

The amount of direction or guidance and the Presence and absence of working examples.

The specification teaches detection of D12S1657, D12S393, D12S1706, and D12S346 for diagnosis of melanoma, breast, or colon cancer. The specification sets forth no other uses for the claimed invention.

The specification teaches there is an unexpected LOH of markers for 12q22-23 in accellular samples (see page 3, lines 5-8). The specification further teaches that the 12q22-23 region encompasses the APAF-1 locus (see page 9, line 26) and there was a statistically significant allelic imbalance in metastatic tumors and primary melanoma ($p=0.02$)(see page 9, lines 28-29). Further APAF-1 loss was significantly correlated with a worse prognosis ($p<0.05$) (see page 10, 1st line). The specification further teaches melanoma patients that responded to chemotherapy had a significantly lower frequency of allelic imbalance at 12q22-23 ($P<0.029$) and better prognosis ($p<0.046$) (see page 10 line 12-13), then patients with an allelic imbalance. Further the specification teaches the use of 12q22-23 markers: D12S1657, D12S393, D12S1706, and D12S346.

The specification teaches LOH frequencies in primary melanomas tissue samples were 20%, 31%, 13% and 17% at D12S1657, D12S393, D12S1706, and D12S346, respectively (see table 1). The specification teaches LOH frequencies in metastatic melanomas were 23%, 35%, 17% and 21% at D12S1657, D12S393, D12S1706, and D12S346, respectively (see table 1). The specification asserts that there is a higher frequency of allelic imbalance in metastatic melanoma than primary melanoma (P=0.02), although there is no frequency differences between stage III melanoma and stage IV melanoma (see page 24,line 11 to page 15 line 1).

The specification further teaches there is no correlation between APAF-1 status and overall survival in primary melanoma tissue samples, but there is a statistically significant correlation between APAF-1 status and Stage III/IV melanoma (p=0.05) (see page 26, lines 10-15). Further survival of stage III metastatic melanoma and stage III metastatic melanoma with RLM was statistically correlated with APAF-1 status (P=0.03, p=0.02) but metastatic melanoma with ILM was not (p=0.17) (see page 26 line 25-page 26 line 3). It thus appears that LOH of D12S1657, D12S393, D12S1706, and D12S346 is correlated with survival of patients with stage III metastatic melanoma with RLM, but not survival with stage III metastatic melanoma with ILM. The specification is silent on LOH of D12S1657, D12S393, D12S1706, and D12S346 and stage IV melanoma.

Further the specification teaches the effect of allelic 12q22-23 in serum samples on melanoma patient outcomes. The specification teaches a significant relationship of allelic imbalance of D12S1657, D12S393, D12S1706, and D12S346 markers (p=0.029) before chemotherapy in the responder group (5 of 24), but not in the responder group

after chemotherapy (9 of 24) (see page 36, line 11-15). It thus appears that chemotherapy resulted in 4 subjects having an LOH of the recited alleles in response to the biochemotherapy (see page 36, line 11-15). While 11 of 20 the non-responders had allelic imbalance before therapy, while only 7 of the 20 had allelic imbalance after therapy(see page 36, line 11-15). These teachings suggest that in 4 non-responders allelic imbalance can be restored in response to biochemotherapy.

Further patients with D12S1657, D12S393, D12S1706, and D12S346 LOH had a statistically significantly worse survival rate ($p=0.046$) (see page 36, line 17) than allelic imbalance negative subjects. The specification teaches response to dacarbazine (DTIC), cisplatin, vinblastin, interferon .alpha.-2b, IL-2, and tamoxifen was related to survival ($p<0.001$) (see page 36, line18).

The specification teaches only concurrent BC regimen of dacarbazine(DTIC), cisplatin, vinblastin, interferon .alpha.-2b, IL-2, and tamoxifen (see page 31, lines 13-17).

The specification does teach a statistically significant association of 12q22-23 LOH and melanoma, therapeutic response and outcome, but the specification teaches there is not a statistically significant relationship after chemotherapy, making the marker unpredictable for melanoma in those cases.

The specification does teach LOH in tumor samples of D12S1657, D12S393, D12S1706, and D12S346 are associated with melanoma and its progression and outcome. The specification teaches that the recited markers are associated with melanoma in primary tumors. The specification further teaches LOH of D12S1657,

D12S393, D12S1706, and D12S346 is correlated with response in serum samples, before but not after chemotherapy.

Although the specification teaches LOH of D12S1657, D12S393, D12S1706, and D12S346 in de-proteinized blood is correlated with the resistance to biochemotherapy of melanoma, the specification provides no support that LOH of the recited alleles in urine, sputum, sperm, etc is correlated with melanoma, breast cancer, or colon cancer. The specification teaches," it has been established that markedly increased concentrations of soluble DNA are present in plasma of individuals with cancer and some other diseases, indicating that cell free serum or plasma can be used for detecting cancer DNA with microsatellite abnormalities" (see page 8, lines 10-15). The specification appears to suggest that the accellular DNA is released into the serum or plasmid, however it does not teach or suggest the DNA from melanoma, breast or colon cancer would be present in sperm, feces, sputum, etc. It would thus be unpredictable to make such an association.

The state of prior art and the predictability or unpredictability of the art:

The prior art teaches that LOH D12S1657, D12S393, D12S1706, and D12S346 is common in metastatic melanoma (see abstract, Soegnas, et al Nature, 2001, vol 409, 207-211). The prior art teaches D12S1657, D12S393, D12S1706, and D12S346 LOH is indicative of poor response to chemotherapy, (see page 209, column 1, lines 8-10). The prior art does not teach a correlation between D12S1657, D12S393, D12S1706, and D12S346 LOH and any cancer other than melanoma.

Gocke et al (US Patent 6156504, issued Dec 5, 2000) teaches methods of using of extracellular DNA found serum (2, 7) or plasma (claims 3,8,) for the detection of cancer (see title, abstract). Gocke teaches peripheral blood (claims 81, 82,); plasma or serum is easily accessible and amenable for DNA amplification (see column 2, lines 54-55). Gocke et al further teaches that many studies have used nucleic acid amplification to detect intracellular DNA extracted from circulating cells in blood (see column 2, line 56-60). Gocke teaches use of blood, plasma, or serum allows rapid and timely extraction and sensitive detection of extra cellular tumor associated or extracellular mutated oncogenic DNA (see column 3, lines 60-63).

Fujiwara et al (Cancer Research (1999) volume 59, pages 1567-1571)teaches naked DNA released from tumor cells is released, enriched and remains stable in the blood of cancer patients and used for detecting cancer specific DNA markers (1567, 1st column, bottom). Fujiwara teaches genetic changes resulting progression of melanoma from stage II to stage IV are not well understood (1567, 2nd column, 2nd full paragraph). Fujiwara teaches multiple LOH markers can be detected in the plasma of melanoma patients, but not healthy donors (1567, 2nd column, 2nd full paragraph). Fujiwara teaches, “The study also demonstrated that melanomas release tumor specific genetic markers in the blood that correlated to the patients respective melanoma legion" (1567, 2nd column, last paragraph). Fujiwara further teaches the frequency and number of microsatellite markers with LOH in plasma significantly increased in more advanced clinical stages of the (page 1570, 2nd column, 3rd paragraph). Fujiwara further teaches, “This study illustrates the clinical use or microsatellite analysis in detecting tumor DNA

in plasma of melanoma patients. The analysis of LOH in plasma provides a logistically practical assay to monitor genetic changes during melanoma progression. The study demonstrates that at early clinical stages, release of DNA (LOH marker) is limited. Plasma LOH analysis may be more suitable to monitor stage II to stage IV progression before and during therapy as well as during post treatment 'follow-up. The markers may be also useful to detect subclinical disease recurrence in disease-free patients. Tumor progression is dynamic, and the genetic changes that concurrently occur are also ongoing. The most significant advantage of this approach in assessing plasma compared with direct analysis of tumor biopsies is the ability to monitor disease progression and genetic changes without assessing the tumor. This is particularly important during early phases of distant disease spread in which subclinical disease is undetectable by conventional imaging techniques. “ Thus Fujiwara does not suggest that use LOH of accellular DNA markers is unpredictable, but suggests their use. Further Fujiwara teaches, " We and others have examined molecular markers such as melanoma- associated antigen mRNA markers in RT-PCR assays to detect melanoma cells in blood, lymph nodes, and various other organs. These molecular markers have been shown to be very useful in detecting metastatic melanoma cells and disease progression.” Page (1570, 1st column). Fujiwara teaches LOH was a 50% reduction in the intensity of the allele relative to a normal matched lymphocyte (1568, 1st column). Fujiwara teaches the D3S1293 LOH is associated with disease progression.

O'Day et al (Journal of Clinical Oncology (1999) volume 17, pages 2752-2761)) teaches that different mono-therapies and combination therapies have different response rates.

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed one of skill in the art would first have to determine if it would be predictable to practice the invention relative to any control sample from any biological fluid or tissue from a "normal" subject. Thus would be unpredictable as the specification teaches that LOH was not found in the blood of a "normal subject." Further the specification and prior art has provided no evidence that the a control DNA from urine, hair, feces, etc have the DNA marker at the diploid level so as to allow one of skill in the art to determine a LOH such as to practice the invention as claimed. Further it would be unpredictable as the specification provides no guidance as to what a "control human DNA" requires.

Further it would be unpredictable to detect responsiveness to any chemotherapy, radiation therapy, gene therapy, immunotherapy or surgical procedure as O'day et al teaches different chemotherapy agents have different response rates. Further the specification only provides data toward the efficacy of dacarbazine(DTIC), cisplatin, vinblastin, interferon .alpha.-2b, IL-2, and tamoxifen. Thus it would be unpredictable to use the claimed markers to determine efficacy of any cancer therapy without specific evidence. Further the only data about survival is following treatment with

dacarbazine(DTIC), cisplatin, vinblastin, interferon .alpha.-2b, IL-2, and tamoxifen, thus it would be unpredictable to determine any survival as the specification and prior art lack any evidence the survival is increased in a subject without the treatment.

Therefore, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

The response traverses the instant rejection. The response asserts that amendment of the claim to require “control human DNA” has overcome this aspect of the rejection. The response substantially reiterates the arguments presented by applicant Hoon in his declaration. These arguments have been addressed above in response to the argument. The response asserts, "control DNA from a normally healthy individual or a normal cell would be diploid (two copies) for the marker, which one of skill in the art could readily compare to a subject’s sample DNA which could either be diploid (two copies) or show LOH (on copy). “ This argument has been thoroughly reviewed but is not considered persuasive as the claims require "control human DNA." Thus the claims do not require DNA from a healthy individual or DNA that is diploid as asserted. Thus based on the teachings of Fujiwara that accellular DNA from subjects with cancer can be 2 to 4 fold greater than normal controls the invention would be unpredictable, as human accellular control DNA from a cancer patient would more than

likely demonstrate any healthy subject has LOH relative to the accellular DNA that is 2 to 4 fold greater than normal.

The response continues by again asserting control DNA is from a normal subject and is diploid. These arguments are assertions of counsel that have not been substantiated by evidence. Control human DNA in the absence of any definition in the specification can be from any human subject or any source, including subjects with cancer, or a monoploid sample produced in the lab. These are also arguments to limitations that are not present in the claims. Thus these arguments are not persuasive. First, MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant."

This should not be construed as an invitation for providing evidence. As further stated in the MPEP 716.01 regarding the timely submission of evidence:

A) Timeliness.

Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. In re Rothermel, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted:

(1) prior to a final rejection,

(2) before appeal in an application not having a final rejection, or

(3) after final rejection and submitted

(i) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection, or

(ii) with a satisfactory showing under 37 CFR 1.116(b) or 37

CFR 1.195, or

(iii) under 37 CFR 1.129(a).

With respect to the biochemotherapy and responsiveness to cancer the response asserts that one of skill in the art could understand and apply the findings to other treatments of metastatic tumors. These are again arguments of counsel that have not been substantiated by any evidence. The teachings of O'Day and Healy demonstrate that different treatment regimens for melanoma have different results, thus making it unpredictable to extrapolate from one treatment to another.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 103-117, 119-126, 128-132, are rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al (Nature, 2001, volume 409, pages 207-211) in view of Fujiwara et al (Cancer Research (1999) volume 59, pages 1567-1571).

Soengas et al teaches detection of loss of heterozygosity of 12q22-23 region in 24 patients using 6 12q22-23 microsatellite markers including D12S1657, D12S393, D12S1706, and D12S346 (see figure 1 and legend). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR.

Soengas teaches loss of microsatellite markers (D12S1657, D12S393, D12S1706, and D12S346) in the 12q22-23 regions in patients are detected in metastatic melanoma (see abstract; page 207 2nd column, lines12-14). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR. Soengas teaches LOH of markers D12S1657, D12S393, D12S1706, and D12S346 is associated with loss of APAF1 expression (page 210, 2nd column).

Soengas teaches there is a high rate of APAF-1 LOH in metastatic melanoma (see page 207, column 2, lines 17-19), but not in primary melanoma (see page 208, 1st column, line 1). Soengas thus teaches LOH of APAF-1 in melanoma indicates a high probability of metastatic cancer.

Soengas teaches loss of APAF-1 is associated with disease progression (see page 208, lines 2-4).

Soengas teaches there is correlation of APAF-1 levels and response to Adriamycin in melanoma cells (see page 209, column 1, lines 8-10). Soengas teaches that APAF-1 levels are lower in melanomas with APAF-1 LOH. Soengas thus teaches APAF-1 LOH results in poor efficacy of treatment in melanoma.

Soengas does not teach the use of accellular DNA from plasma, serum, or blood as a sample.

However, Fujiwara teaches naked DNA released from tumor cells is released, enriched and remains stable in the blood of cancer patients and used for detecting cancer specific DNA markers (1567, 1st column, bottom). Fujiwara teaches genetic changes resulting progression of melanoma from stage II to stage IV are not well understood (1567, 2nd column, 2nd full paragraph). Fujiwara teaches multiple LOH markers can be detected in the plasma of melanoma patients, but not healthy donors (1567, 2nd column, 2nd full paragraph). Fujiwara teaches, “The study also demonstrated that melanomas release tumor specific genetic markers in the blood that correlated to the patients respective melanoma legion" (1567, 2nd column, last paragraph). Fujiwara further teaches the frequency and number of microsatellite markers with LOH in plasma significantly increased in more advanced clinical stages of the (page 1570, 2nd column, 3rd paragraph). Fujiwara further teaches, “This study illustrates the clinical use or microsatellite analysis in detecting tumor DNA in plasma of melanoma patients. The analysis of LOH in plasma provides a logistically practical assay to monitor genetic

changes during melanoma progression. The study demonstrates that at early clinical stages, release of DNA (LOH marker) is limited. Plasma LOH analysis may be more suitable to monitor stage II to stage IV progression before and during therapy as well as during post treatment 'follow-up. The markers may be also useful to detect subclinical disease recurrence in disease-free patients. Tumor progression is dynamic, and the genetic changes that concurrently occur are also ongoing. The most significant advantage of this approach in assessing plasma compared with direct analysis of tumor biopsies is the ability to monitor disease progression and genetic changes without assessing the tumor. This is particularly important during early phases of distant disease spread in which subclinical disease is undetectable by conventional imaging techniques. " Thus Fujiwara does not suggest that use LOH of accellular DNA markers is unpredictable, but suggests their use. Further Fujiwara teaches, " We and others have examined molecular markers such as melanoma- associated antigen mRNA markers in RT-PCR assays to detect melanoma cells in blood, lymph nodes, and various other organs. These molecular markers have been shown to be very useful in detecting metastatic melanoma cells and disease progression." Page (1570, 1st column). Fujiwara teaches LOH was a 50% reduction in the intensity of the allele relative to a normal matched lymphocyte (1568, 1st column). Fujiwara teaches the D3S1293 LOH is associated with disease progression.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Soengas method of detecting markers D12S1657, D12S393, D12S1706, and D12S346 by use of peripheral blood,

plasma, or serum as taught by Fujiwara, for detection of markers associated with melanoma progression because Fujiwara teaches blood, plasma, or serum is easily accessible and amenable for DNA amplification and thus detection of nucleic acids. The ordinary artisan would further be motivated because, Fujiwara teaches, "The most significant advantage of this approach in assessing plasma compared with direct analysis of tumor biopsies is the ability to monitor disease progression and genetic changes without assessing the tumor. This is particularly important during early phases of distant disease spread in which subclinical disease is undetectable by conventional imaging techniques." Thus as Fujiwara teaches methods of nucleic acid analysis by PCR amplification as taught by Soengas the artisan would have a reasonable expectation of success. The combination of Soengas and Fujiwara would have resulted in a method of detecting the LOH of multiple markers including D12S1657, D12S393, D12S1706, and D12S346 in accellular DNA from blood, serum, or plasma and from this detection allow prediction of probability of survival, prognosis, efficacy and response to therapy as Soegnas teaches the loss is associated with a loss of response to chemotherapeutic agents and Fujiwara teaches increasing LOH results in poor prognosis and is associated with more advanced melanoma.

Response to Arguments

The arguments with respect to the Declaration by Dr. Hoon have been addressed above.

The response correctly identifies that Soegnas does not specifically teach the detection of accellular markers. The response continues by indicating the Fujiwara does not teach the elected combination of markers.

The response continues by asserting, "the focus of Soegnas is Apaf-1 expression and LOH, not LOH of DNA markers D12S1657, D12S393, D12S1706, and D12S346." This argument has been thoroughly reviewed but is not considered persuasive as Soegnas in Figure 1 is examining LOH of D12S327, D12S1657, D12S393, D12S1706, and D12S346. Soegnas further indicates the LOH of the examined markers are found in metastatic, but not primary melanoma. Further Soegnas teaches that decreased expression of the genes in the area of LOH is associated with resistance to chemotherapy. Thus Soegnas teachings are not limited to Apaf-1 as asserted.

The response again asserts that Soegnas does not teach detection of the claimed markers from accellular DNA. The examiner concurs as the rejection would be anticipatory. The response then returns to the arguments of the declaration which are not persuasive for the reasons addressed previously.

The response asserts that the rejection has two flawed assumptions. First the LOH of metastatic tumors can predict therapeutic value. This argument has been thoroughly reviewed but the broadest claim is to survival or efficacy not therapeutic value. Further, one of skill in the art realizes that LOH of microsatellite markers found only in metastatic melanoma indicates a worse survival or prognosis.

The response then reiterates the arguments of the declaration with respect to Fujiwara. The response appears to be asserting that LOH is found in a primary tumor is

not necessarily found in accellular DNA. This argument has been thoroughly reviewed but is not considered persuasive as the teachings of Soegnas are to metastatic melanoma. Further the claims are not limited to a single marker but a combination of one or more and applicant's own work as presented in the references of Taback and Fujiwara teaches that increased LOH in accellular DNA is known to be associated with later stage disease. Thus these arguments are not persuasive.

The response continues by reviewing the teaching of Taback. The response indicates that Taback indicates that detecting LOH of D9S157 in primary tumors was not of prognostic value. This argument has been thoroughly reviewed but is not considered persuasive as the findings that Taback describes are relative to primary tumors, while the teachings of Soegnas are in metastatic tumors. Further as indicated previously applicant as a co-author of the papers of Taback and Fujiwara indicate that the more accellular LOH in a melanoma patient the worse the disease stage, which in melanoma is correlated with prognosis and therapy accellular. The response continues by asserting that LOH in primary and metastatic tumors is not predictable of accellular LOH. These again are arguments of counsel that have not been substantiated by evidence. Further Dr. Hoon's instant declaration indicates increasing accellular LOH is correlated with later stage melanoma. Further the teachings of Fujiwara stating, "the frequency and number of microsatellite markers with LOH in plasma significantly increased in more advanced clinical stages of disease" (1570). The arguments with respect to Taback are not persuasive as Taback states, "We and others have shown that as melanomas progress they acquire additional LOH events, which may be

associated with a metastatic or more aggressive phenotype" (5725). Taback teaches there is a 91% correlation between plasma LOH marker detected and LOH in the corresponding tumor specimen was observed (5725).

Thus as the response has provided no secondary consideration demonstrating secondary considerations for the claim, the rejection is maintained.

8. Claims 118 and 127 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al (Nature, 2001, volume 409, pages 207-211) in view of Fujiwara et al (Cancer Research (1999) volume 59, pages 1567-1571) as applied to claim 103-117, 119-126, 128-132, above, and further in view of Chapman et al (Journal of Clinical Oncology.(1999) volume 17, pages 2745-2751), Healy (oncogene (1998) volume 16, pages 2213-2218) and O'Day et al (Journal of Clinical Oncology (1999) volume 17, pages 2752-2761).

The claim 118 and 127 are drawn to biochemotherapy being selected from a group consisting of dacarbazine, cisplatin, vinblastin, interferon alpha-2b, IL-2, and tamoxifen.

The teachings of Fujiwara and Soegnas are set forth above.

Soengas and Fujiwara do not teach that loss of heterozygosity of D12S1657, D12S393, D12S1706, and D12S346 is predictive of response to biochemotherapy or predicted efficacy of response to biochemotherapy from the group consisting of dacarbazine, cisplatin, vinblastin, interferon alpha-2b, IL-2 and tamoxifen.

However, Soengas teaches "Assessment of Apaf-1status may therefore improve the therapeutic management of patients with malignant melanoma" (see page 210, 2nd column last line of text).

Chapman teaches, " patients with stage IV melanoma, based on American Joint Committee on Cancer (AJCC) criteria, have a universally poor prognosis with a median survival time of 3 to 11 months, depending on subgroup analyzed" (page 2745, 1st column). Chapman teaches, "Although initial response rates have often been encouraging in single-institution trials (typically 40% to 50%), subsequent phase II trials have not confirmed these response rates,9-14 and prospective phase III trials failed to demonstrate a superiority of many of these regimens over dacarbazine alone" (page 2745, 1st column). Chapman further teaches, "Patients with metastases confined to soft tissue sites (skin, lymph nodes, or lung) are more likely to respond to chemotherapy and, in many databases, have a better prognosis than patients with metastases to other sites. Of the 226 patients assessable for tumor response, 99 (44%) had metastasis confined to soft tissue sites. In this group of patients, the response rate to the Dartmouth regimen was higher than the response rate to dacarbazine (32% v 14%), with the difference reaching statistical significance. Despite a higher rate of tumor

responses in patients with soft tissue metastases treated on the Dartmouth arm, there was no improvement in overall survival. This is not surprising given that, in both treatment arms, the response rates were relatively low and there were no complete responses. The European Organization for Research and Treatment of Cancer Melanoma Cooperative Group has reported a similar observation in which interleukin-2–based treatments doubled the response rate but had no apparent impact on survival.31 Other subsets of patients were analyzed (women and patients with visceral metastases), but no increase in response rate or survival was observed for the Dartmouth arm" (page 2750, 1st column). Thus Chapman teaches that subjects with stage IV melanoma have a poor response to treatment, poor survival time, and thus poor efficacy of response to treatment, although those with soft tissue metastasis were more likely to respond to treatment.

Healy teaches, "Some (but not all) studies on DNA ploidy in melanoma have suggested that individuals with tumours exhibiting aneuploidy have a poorer out-come" (page 2213, 2nd column, last paragraph). Healy further teaches, "metastatic melanoma is a late stage of disease, and nearly all patients with metastases will eventually die from their melanoma" (page 2213, 2nd column, last paragraph). Healy further teaches, "However, based on the FAL scores, the results suggest that the overall level of genomic instability (as well as losses of 6q and 10q) may determine the clinical behavior of the melanoma and the ultimate clinical survival. This association of higher FAL scores with a poorer clinical, outcome, independent of the depth of invasion,

suggests that this variable might allow the identification both of individuals with thin melanomas who will eventually die from their tumour and of subjects with paradoxically thick melanomas in whom the melanoma will not metastasize." (page 2215, 2nd column, last paragraph).

Further O'Day et al teaches "5-day modified concurrent biochemotherapy regimen of dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alpha-2b, and tamoxifen was repeated at 21-day intervals" (see abstract). O'Day teaches pretreatment evaluation (page 2753, 2nd column). O'Day further teaches, "the concurrent biochemotherapy regime of Legha et al was modified in an effort to reduce toxicity further while maintaining or improving efficacy. These modifications consisted of decrescendo IL-2 dosing, routine use of growth factor support with granulocyte colony-stimulating factor (G-CSF), and low-dose tamoxifen. The total IL-2 dose was unchanged, but this agent was administered in a decrescendo schedule, with a higher initial dose in the first 24 hours that decreased progressively on subsequent days. This change in IL-2 dosing is based on preclinical and clinical studies suggesting that decrescendo dosing improves efficacy and reduces cumulative IL-2 toxicity.29, 30 Routine post treatment G-CSF was implemented because of the high incidence of grade myelosuppression, fever/neutropenia, and infection in Legha's concurrent biochemotherapy trial. Tamoxifen was added to the regimen because at the time the study was designed, data suggested potential synergistic effects with chemotherapy" (page 27531st column, 2nd full paragraph).

Therefore, it would be prima facie obvious to one of skill in the art at the time the invention was made to predict long term survival (efficacy of response) of stage IV melanoma to dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alfa-2b, and tamoxifen in patients or the probability of responsiveness to dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alfa-2b, and tamoxifen in view of the teachings of Soengas and Fujiwara with a reasonable expectation of success. Chapman and Healy teach that subjects with stage IV melanomas and metastasis had poor longer term prognosis and thus poor response to biochemotherapy. Chapman teaches only 5% to 20% of subjects with stage IV melanoma responded to biochemotherapy, while Healy teaches genomic instability plays a large role in clinical outcome. The teachings of Soengas suggest that loss of heterozygosity of D12S1657, D12S393, D12S1706, and D12S346 markers results decreased apoptosis, which in turn results in increased chemoresistance to chemotherapeutic agents in melanoma. Thus, it would have been obvious to one of skill in the art that subjects with stage IV melanoma and LOH of markers known to be associated with decreased apoptosis in melanoma in response to treatment a chemotherapeutic drug (adriamycin) would also be associated with decreased apoptosis and thus chemoresistance to other known chemotherapeutic agents (dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alfa-2b, and tamoxifen). It would have been obvious to one of skill in the art in view of the teachings of Soengas and O'Day to use D12S1657, D12S393, D12S1706, and D12S346 to predict responsiveness or efficacy of treatment as Soengas teaches "Assessment of Apaf-1status may therefore improve the therapeutic

management of patients with malignant melanoma" (see page 210, 2nd column last line of text). The artisan would be motivated because Soengas and Fujiwara suggest such a method as cited above. The artisan would have a reasonable expectation of success as the artisan would merely be using an assay to predict the response to a known biochemotherapy.

Response to Arguments

The response reiterates the arguments previously presented with respect to Soegnas and Fujiwara. These arguments have been previously addressed.

Summary

No claims are allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN POHNERT whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Steven C Pohnert/
Primary Examiner, Art Unit 1634